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Setting Priorities for Diabetic Retinopathy Clinical Research and Identifying Evidence Gaps

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Abstract

Purpose—Prioritizing comparative effectiveness research may contribute to obtaining answers that clinicians perceive they need and may minimize research that could be considered wasteful. Our objective was to identify evidence gaps and set priorities for new systematic reviews and randomized controlled trials for managing diabetic retinopathy (DR), including diabetic macular edema (DME).

Design—Cross-sectional study.

Participants—Diabetic Retinopathy Clinical Research Network (DRCR.net) investigators.

Methods—We provided recommendations from the American Academy of Ophthalmology's 2012 Preferred Practice Patterns for Diabetic Retinopathy as 91 answerable clinical research questions about intervention effectiveness to 410 DRCR.net investigators to rate each question's importance from 0 (not important) to 10 (very important) using a 2-round Delphi survey and to suggest additional questions. We considered questions as high priority if at least 75% of respondents to both rounds assigned an importance rating of 5 or more in round 2. We also extracted outcome measures relevant to DR and asked respondents to identify those that must be measured in all studies. We mapped Cochrane reviews published up to March 2016 to high-priority clinical research questions.

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Author Contributions:

Conception and design: Hutfless, Li, Bressler, Bittner, Glassman, Dickersin

Analysis and interpretation: Le, Hutfless

Data collection: Hutfless, Heyward

Obtained funding:

Overall responsibility: Le, Hutfless, Li, Bressler, Heyward, Bittner, Glassman, Dickersin

Main Outcome Measure—Ranking of importance of each clinical question.

Results—Thirty-two individuals completed rounds 1 and 2 and suggested 15 questions. Among the final list of 106 clinical research questions, 22 questions met our definition of high priority: 9 of 22 concerned the effectiveness of anti-VEGF therapy, and 13 of 22 focused on how often patients should be followed up (re-examination) and treatment effectiveness in patients with specific characteristics (e.g., DME). Outcomes that 75% or more of respondents marked as “must be measured in all studies” included visual acuity and visual loss, death of participants, and intraocular pressure. Only 1 prioritized question was associated with conclusive evidence from a Cochrane systematic review.

Conclusions—A limited response rate among [DRCR.net](#) members identified 22 comparative effectiveness research questions as high priority for the management of DR, including DME, but few were associated with Cochrane reviews. These results support the need of systematic reviews and randomized controlled trials to address evidence gaps.

Research that addresses real-world clinical questions may help patients and providers make evidence-informed healthcare decisions.^{1,2} In 2011, the Institute of Medicine recognized the critical role of systematic reviews of comparative effectiveness research to provide the best evidence for clinical decision making.² Because synthesis of all available evidence in a systematic review is resource intensive,³ many have recognized the critical importance of prioritizing performance and updates.^{1,4–6} Prioritization also reduces unnecessary duplication and failure to build on findings from previous research, both representing considerable waste.⁴

Recognizing that there are many options for prioritizing clinical research needs,^{1,5–9} our group developed an alternative framework that we have used in the context of eye and vision topics.^{10–12} We begin by identifying research questions addressed in clinical practice guidelines and then asking clinicians to rate the importance of having an answer to the stated research question.^{1,11} The advantage of this model is that it assumes that the clinical practice guidelines address the many topics that specialists confront in real-world medical practice.

In the current project, we set out to prioritize systematic review topics for diabetic retinopathy (DR), including diabetic macular edema (DME).^{13–16} In 2010, an estimated one third of the 285 million individuals with diabetes worldwide had documented signs of DR. Of those with DR, one third have vision-threatening conditions, including proliferative DR (PDR) or DME.¹⁷ In the United States, the number of people with DR is expected to nearly double from 7.7 million in 2010 to 14.6 million by 2050.^{9,18}

Our objective was to set priorities for new systematic reviews and randomized clinical trials of the management of DR and DME using topics identified from the American Academy of Ophthalmology’s (AAO) Diabetic Retinopathy Preferred Practice Patterns (PPP) and a 2-round survey of members of the Diabetic Retinopathy Research Network ([DRCR.net](#)).^{19,20} We matched high-priority questions with existing evidence from Cochrane reviews to identify evidence gaps.

Methods

Our research involved 8 key steps (see Fig 1). The Johns Hopkins Bloomberg School of Public Health Institutional Review Board classified our proposed research activity as meeting the criteria for exemption under 45 CFR 46.101(b), category 2.

Identification of Recommendations

In December 2013, we extracted verbatim text from the 2012 PPP that could be considered as a recommendation for care. For each statement, we noted the patient population to which it applied (e.g., a recommendation for patients with nonproliferative DR and PDR, or for patients with DR with or without the presence of clinically significant DME). We also extracted the guideline panel's assessment of the importance of the recommendation and the strength of the evidence supporting it. Most recommendations in the 2012 PPP were not accompanied by references to systematic reviews. The PPP Retina/Vitreous panel included 8 ophthalmologists and 1 methodologist.

Restating and Refining the Recommendations as Research Questions and Identification of Outcomes

We restated each recommendation as a clinical research question. In keeping with the previous studies using a similar framework,^{11,12} we did not include guideline statements on disease definition, disease cause, diagnostic test accuracy; statements classified as ethical or legal statements; or statements that were not recommendations. We also did not specify the outcomes in the clinical research questions, recognizing that the goals of interventions may vary by stage of diabetic retinopathy. Further, it is the responsibility of the investigative group to define key efficacy and safety criteria and study objectives. Two investigators extracted all clinical outcome measures described as pertaining to DR and DME and resolved disagreements through discussion.

A retinal specialist (N.M.B.) from the [DRCR.net](#) examined and edited the questions, using the original 2012 PPP text for comparison. He suggested revisions to capture concepts that were current and relevant to care at the time of his review (June 2014). Given the rapid changes occurring in the management of DR, including DME, with the advent of intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents and corticosteroids, questions were modified by one of us (N.M.B.) to capture all but 2 recommendations from the 2014 PPP in the survey.

Identifying Survey Recipients

We elected to survey [DRCR.net](#) members. The [DRCR.net](#) is a collaborative network of clinicians and retinal specialists dedicated to supporting multicenter clinical research on diabetes-induced retina disorders.¹⁹ At the time of the survey, there were 410 [DRCR.net](#) investigators from 140 different sites in 36 different states.

Round 1 of the Survey

We developed an online survey instrument using Survey Monkey ([SurveyMonkey.com](#) LLC, Palo Alto, CA). Round 1 of our modified Delphi survey included 4 separate groups of

questions: (1) to confirm participant understanding of the purpose of the survey (Supplemental Table 1, available at www.opthalmologyretina.org), (2) to obtain respondent characteristics, (3) to prioritize the 91 clinical research questions (Supplemental Table 2, available at www.opthalmologyretina.org), and (4) to prioritize 31 DR-related outcomes.²¹

For each clinical research question, we asked participants to “rate the importance of having an answer to the above clinical question” for patients with a particular severity of DR or DME (e.g., severe nonproliferative DR, non–high-risk PDR), using an 11-point scale from 0 (not important at all) to 10 (highly important). Respondents had the option of selecting “no judgment” or proceeding to the next question without responding (Supplemental Fig 1, available at www.opthalmologyretina.org). In round 1, we also invited respondents to write in clinical research questions that they believed were important but that had not been addressed in the preceding list of questions. We did not restrict the types of questions participants could suggest. For each of the 31 outcomes, we asked participants to “rate the importance of measuring each when studying DR using a 3-point scale: must measure in all studies, measure for studies of some interventions, or not important to measure in the majority of studies.”

In September 2014, the DRCR.net coordinator (A.G.) e-mailed its 410 members with links to the round 1 survey. The e-mail included the initial invitation letter and consent information. The surveys were sent out in 2 batches, with half of the e-mail list receiving the survey with questions in reverse order. We sent 1 reminder and accepted responses up to 8 weeks after e-mailing round 1.

Round 2 Survey

In round 2, we addressed a concern expressed by some members of the DRCR.net community to 1 of the authors (N.M.B.) that certain clinical research questions related to interventions that were no longer commonly used in practice. Accordingly, we strengthened an existing statement in the preamble noting this fact and made other minor wording changes to improve clarity. This revision process led to longer questions. The round 2 questionnaire comprised 106 clinical research questions (i.e., 91 questions from round 1 and 15 additional questions suggested by respondents; Supplemental Table 3, available at www.opthalmologyretina.org) and the same 31 outcomes. Round 2 instructions asked participants to rerank each question by taking into account the responses by their peers in round 1 (we used histograms to summarize all response). In February 2015, we sent the round 2 survey (same survey to all 410 DRCR.net members) and sent 1 reminder that allowed 1 month for a response.

Prioritization of Clinical Research Questions and Outcomes

Given the distributions of importance ratings that we observed, we elected to use the median score and the twenty-fifth and seventy-fifth percentiles of the ratings (rather than the mean) as a measure of variability for each clinical question. We used boxplots to analyze round 2 responses of those who responded to both rounds 1 and 2. Questions were considered moderately important if 75% or more respondents assigned a rating of 5 and important if 75% or more respondents assigned a rating of more than 5.¹² We used a similar approach to

prioritize the 31 outcomes, considering them to be important if 75% or more of respondents assigned the highest rating of “must measure in all studies.” All data provided, unless otherwise stated, refers to those who responded to both rounds 1 and 2.

Evaluation of Response Patterns by Participant Characteristics

We calculated the proportion of respondents who correctly completed the survey and compared respondent characteristics for those who completed round 1 only and those who completed both rounds 1 and 2 using Pearson’s chi-square test. We compared respondent characteristics of our survey respondents with the available characteristics of [DRCR.net](#) members. We examined the response distribution patterns for all 106 questions in round 2, including the frequency that each rating was assigned and the shape of the histograms generated from responses. To assess whether ratings varied by respondent characteristics, we compared means of the within-individual variability and the associated 95% confidence intervals. All analyses were conducted using Stata software version 14 (StataCorp, College Station, TX)²² and SAS software version 9 (SAS Institute, Inc, Cary, NC).²³

Comparison of High-Priority Questions with the Importance Rating Assigned in American Academy of Ophthalmology Guidelines

We compared the clinical research questions classified as moderately important and important with the corresponding rating of “importance to the care process” in the 2012 PPP.

Comparison of the Prioritized Clinical Questions with Existing Cochrane Systematic Reviews

To examine which prioritized questions are associated with existing evidence supporting a clinical recommendation, we conducted a search on March 16, 2016, for all Cochrane systematic reviews with DR or DME specified as the condition of study, using the Cochrane Eyes and Vision database (<http://eyes.cochrane.org/our-reviews>) and Cochrane’s centralized database of reviews and other documents (<https://archie.cochrane.org/>). We mapped prioritized clinical research questions to Cochrane systematic reviews identified by our search.

Results

Participant Characteristics

Of the 410 [DRCR.net](#) investigators invited to participate in the survey, 55 (13.4%) completed round 1 of the survey. Thirty-two of the 55 (58.2%) who completed round 1 also completed round 2 (Table 1). Another 21 [DRCR.net](#) members did not respond to round 1, but responded to round 2. A total of 32 individuals (7.8%) completed rounds 1 and 2 and suggested 15 questions.

Approximately one third of respondents (20/55 [36%]) practiced in an academic or university-based setting, which is comparable with the overall [DRCR.net](#) membership (approximately 32%). Respondents were from 25 of 36 states of the United States comprising [DRCR.net](#) active membership, and no respondents self-identified as practicing in Canada or another country.^{19–24}

We did not observe any differences in the characteristics of those who completed both rounds and those who completed only round 1 but not round 2 (Table 1) or those who completed round 2 but not round 1. The average time spent on round 2 of the survey was approximately 50 minutes.

Clinical Question Prioritization Results

Twenty-two of the 106 clinical research questions (20.7%) in round 2 were assigned a rating of 5 or higher in round 2 of the survey by at least 75% of respondents who answered both rounds (Fig 2; Supplemental Fig 2). Based on the ratings assigned, we considered 9 of 22 questions (40.9%) as important and 13 of 22 questions (59.1%) as moderately important (Table 2). Eleven of the 22 high-priority questions (50%) were suggested by respondents or modified through consultation with the ophthalmologist coinvestigator, and 11 of 22 such questions (50%) were derived directly from the 2012 PPP. Nine of 22 important and moderately important questions concerned anti-VEGF treatment for DR, whereas 13 of 22 questions focused on re-examination and treatment effectiveness in patients with specific characteristics (e.g., DME).

Outcome Prioritization Results

Three outcomes were rated by at least 75% of the respondents as “must measure in all studies.” These outcomes were visual acuity and visual loss, death, and intraocular pressure (Supplemental Fig 3, available at www.ophtalmologyretina.org).

Prioritization Profiles by Respondent Characteristics

We did not identify a particular respondent characteristic that suggested a respondent was more likely or less likely to give higher or lower ratings than another when we evaluated potential associations using the mean of within-individual rating variability (Supplemental Fig 4, available at www.ophtalmologyretina.org).

Comparison of High-Priority Questions to Ratings of Importance Assigned in 2012 American Academy of Ophthalmology Guidelines

When we compared clinical research questions ranked as high priority by survey respondents with the 2012 PPP ratings of importance to the care process, we observed moderate agreement. Six of the 11 high-priority questions (55%) were derived from the 2012 PPP statements associated with a level A rating (most important to the care process); the remaining questions were derived from 2012 PPP statements with no ratings provided (Table 2).

Comparison of the Prioritized Clinical Questions with Existing Cochrane Systematic Reviews

We identified 11 Cochrane reviews for DR and DME.^{14,25–32} One review covered 4 of the 22 high-priority questions, but the authors did not consider the evidence for the use of anti-VEGF for PDR to be conclusive for the subgroup to which the high-priority clinical research questions refer. Another review covered a question added in round 1 by a respondent on optical coherence tomography. Although we did not extract recommendations related to

diagnostic test accuracy, we allowed participants to suggest any type of questions for prioritization. The results in the Cochrane review on optical coherence tomography were considered to be conclusive. Thus, we were able to map 1 of 22 high-priority questions with conclusive evidence from a Cochrane review.

Discussion

Through a 2-round Delphi survey of [DRCR.net](#) members using questions that we derived from the AAO PPP for DR, we derived a ranked list of 22 priority clinical research questions for systematic reviews and comparative effectiveness research related to the management of DR. We determined that almost half of the questions that the respondents ranked as highest priority were related to the effectiveness of anti-VEGF therapy, whereas the outcomes that must always be measured in all studies include visual acuity and visual loss, death, and intraocular pressure. Although our original questions were derived from the 2012 PPP, because we added 15 questions to the survey to increase its relevance to questions that were current at the time of the survey, all but 2 recommendations from the 2014 PPP were included in the survey.

Deriving questions from the PPP for prioritization was challenging because recommendations were scattered throughout the text and tables in the 2012 PPP for DR.²⁰ Although the 2014 PPP collated specific recommendations in an appendix, we noted recommendations appearing elsewhere, such as in the introduction and background where cause is discussed or in the care process text as well.^{20,33} Others have also noted this challenge.³⁴ We suggest assembling all future PPP recommendations in one place. In addition, it would be helpful if statements in the text (that are repeated in the list of recommendations) use wording or are prominently labeled in text as recommendations.

In addition, most recommendations in the 2012 PPP were not accompanied by references to systematic reviews. For example, some recommendations in the Table 6 of the 2012 PPP titled “Management Recommendations for Patients with Diabetes”²⁰ referenced publications reporting 2 clinical trials, 1 from the Retinopathy Clinical Research Network³⁵ and 1 from the Early Treatment Diabetic Retinopathy Study Research group³⁶; others have no accompanying citation. A reference to reliable syntheses takes account of all research meeting minimal quality standards and thus typically is preferable. In the future, comparison of the PPP recommendations with all reliable reviews (including Cochrane reviews) may provide a way to identify reliable evidence supporting the recommendations and evidence gaps.

Core outcome sets, where investigators in a field agree to measure certain trial outcomes in common (they are also free to measure other outcomes), are recommended to assure that results of trials can be compared, contrasted, and combined in systematic reviews.³⁷ This approach can circumvent the resulting missed opportunity that may occur when trials do not measure or report an important outcome, leading meta-analysts to omit the trial from a systematic review.³⁸ Survey respondents selected 3 outcomes derived from the PPP that they considered important to management of DR: visual acuity and visual loss, death, and intraocular pressure. Our findings on outcomes must be explored further to ensure that they

make sense as stated to clinicians and are important to patients.³⁹ For example, the use of visual loss and visual acuity as a single outcome may be problematic. The terms *visual loss* or *vision loss* can be too vague and interpreted inconsistently, that is, they may include loss of vision function perceived by a patient based on visual acuity in both eyes or loss of vision or loss of visual acuity in 1 eye. In addition, although intraocular pressure could be considered a mandatory outcome for assessment, given that intravitreal injections in general can cause an increase in intraocular pressure, it is also possible that respondents interpreted the question to refer to all eye and vision conditions and treatments. Finally, while research groups comprising scientists and clinicians have traditionally decided on the outcomes to be examined in their studies, involving patients in the process is likely to lead to investigating outcomes important to the patients.

Our method to prioritize research questions and outcomes has several unique strengths. First, the modified Delphi method that we used involves formal consensus building among a group of clinicians performing comparative effectiveness research in DR, including DME, across the United States. Second, clinical practice guidelines reflect the clinical community's current state of knowledge and understanding of key issues related to DR, including DME at the time of guideline development. Third, although we originally derived questions from the 2012 PPP by adding and rating questions that were relevant in 2014, the survey respondents updated the rankings to reflect nearly all questions that would have been derived from the 2014 PPP. In addition, the added questions included those on topics we did not address in the round 1 survey such as screening and diagnostic test accuracy.

We encountered several challenges in our study.^{11,12} First, because we relied primarily on interventions and outcomes stated in the guidelines, topics may have been over-represented or underrepresented among clinical research questions that we derived. By providing an opportunity for survey participants to nominate their own research questions, we minimized any priority areas that may have been overlooked. However, because patients were not included as part of the Retina/Vitreous Panel, their views as important stakeholders were not included. Second, the methods used for the survey were not well understood by several [DRCR.net](#) members based on unsolicited feedback to one of the authors (N.M.B.), despite a detailed explanation in the preamble. Third, our response rate to the survey was lower than originally sought (13% of [DRCR.net](#) members responded to round 1, compared with the 20% originally sought), potentially related to the understanding. However, nonresponse bias in surveys conducted among clinicians may be less concerning than in surveys conducted of the general public.^{40–42} It is worth noting that we did not offer any compensation to respondents, and their contribution was entirely voluntary. Fourth, our survey presented a large number of questions, reflecting the large number of recommendations we were able to identify in the 2012 PPP. Although we attempted to decrease the time it would take to respond to our survey by using the umbrella grouping of questions by patient population (e.g., nonproliferative DR vs. non–high-risk PDR vs. PDR patients), the median time it took respondents to complete the survey was almost 1 hour. In another project, we have taken a different approach and are conducting a two-stage survey, first asking a small group to prioritize the many questions we derive from the AAO guidelines, and second asking members of a large specialty society to prioritize the top 10–15 questions. It is worth considering whether a “good” response rate is meaningful in this setting, however, since we

do not expect that prioritization of CEV reviews represents a community's consensus. The review topics we agree to take on are guided by many influences, and given the volunteer nature of our workforce, an individual's preferences are always a factor. [DRCR.net](#) policy states that the Executive Committee will "select and prioritize protocols to be developed following recommendation of the Operations Group and buy-in from investigators".²⁴ Thus, there is nothing in the [DRCR.net](#) policy either requiring or precluding use of the priority list. We look forward to our work contributing to discussion of research prioritization wherever relevant research occurs.

Finally, because we surveyed only [DRCR.net](#) members, we did not solicit priority rankings from patient stakeholders.

We were able to identify 2 reliable systematic reviews (both published after our survey) addressing what our survey respondents told us were important clinical research questions, and 1 of the 2 reviews reported conclusive findings. Although these are only Cochrane reviews and there are likely other reliable systematic reviews addressing these questions, our findings point to a need to assure that the research community, and Cochrane in particular, conduct systematic reviews focusing on high-priority clinical research questions.

In conclusion, we identified 22 high-priority clinical research questions and 3 high-priority clinical outcomes for DR and DME. Most questions represent evidence gaps, with few Cochrane reviews covering the topics. Future PPPs should reference reliable systematic reviews supporting the recommendations and should note evidence gaps. Systematic reviews and clinical trials should be conducted for high-priority questions, a core outcome set for DR—including DME—should be developed, and patient stakeholders should be included in the processes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Drs. Bressler and Glassman are members of DRCR.net and Dr. Dickersin is chair of the DRCR External Protocol Review Committee, reporting to the National Eye Institute.

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Abbreviations and Acronyms

AAO	American Academy of Ophthalmology
DME	diabetic macular edema
DR	diabetic retinopathy
DRCR.net	Diabetic Retinopathy Research Network
PDR	proliferative diabetic retinopathy
PPP	Preferred Practice Patterns
VEGF	vascular endothelial growth factor

- 1) We reviewed the existing 2012 AAO PPP on DR (includes DME) and identified clinical recommendations and outcomes that could be measured in research studies.
- 2) We restated the recommendations into 91 answerable clinical research questions and identified 31 outcomes that could be relevant to DR. We reviewed the list of recommendations, questions, and outcomes with a retina specialist who suggested wording modifications.
- 3) We identified DRCR.net members as appropriate survey participants and developed a survey instrument comprising the 91 questions and 31 outcomes. The two-round survey included two questions to ensure that respondents understood the survey purpose.
- 4) In Round One, we asked the 410 DRCR.net members to assign an importance rating of 0 (low) to 10 (high) to each clinical research question and outcome and to suggest additional questions.
- 5) In Round Two, we asked them to re-rate the questions and outcomes, showing them ratings and comments by their peers.
- 6) We considered a question to be high priority when at least 75% of respondents to both rounds assigned a rating of “5” or higher in Round Two.
- 7) We compared prioritized questions with the AAO PPP’s importance to care ratings.
- 8) We used a database of Cochrane systematic reviews for eyes and vision to match high priority questions to existing evidence supporting a clinical recommendation. This final step allowed identification of CER needs.

Figure 1.

Summary of research methods. Abbreviations: AAO = American Academy of Ophthalmology; CER = comparative effectiveness research; DME = diabetic macular edema; DR = diabetic retinopathy; PPP = Preferred Practice Patterns (for DR).

Figure 2.

Graph showing median ratings and interquartile range of ratings assigned to the 106 clinical research questions, sorted by highest to lowest priority according to the twenty-fifth percentile. The bottom edge of each box represents the twenty-fifth percentile and the top edge represents the seventy-fifth percentile. When the bottom edge of the box for a clinical question is at or above 5, it means that 75% or more of the respondents assigned a rating of 5 or more. Dark blue boxplots correspond to questions rated as important, for which at least 75% of the respondents assigned a rating of more than 5. Light blue boxplots correspond to questions rated as moderately important, for which at least 75% of the respondents assigned a rating of 5. Yellow boxplots correspond to clinical questions for which at least 75% of the respondents assigned a rating less than 5. As a sensitivity analysis, we examined ratings assigned to clinical questions by all participants who responded in round 2, regardless of whether they also responded to round 1, using the same methods and cutoffs. Among all respondents who participated in round 2 ($n = 53$), most (20/22 [90.9%]) high-priority questions were rated as moderately important or important. Two questions (questions 36 and 44) were no longer prioritized as moderately important or important.

Table 1**Respondent Characteristics by Round Completed**

	Respondents Who Completed Only Round One	Respondents Who Completed Both Rounds One and Two	<i>P</i> Value [*]
	<i>n</i> (%)	<i>n</i> (%)	
Answered questions regarding respondent characteristics [†]			
Yes	15 [‡] (65)	30 [‡] (94)	
No	8 (35)	2 (6)	
Primary professional affiliation			0.48
Ophthalmologist	15 (100)	29 (97)	
Other	0 (0)	1 (3)	
Vision specialty area			1.0
Retina	15 (100)	30 (100)	
Primary place of employment			0.66
Private practice/self-employed	8 (53)	14 (47)	
Academia/university	7 (47)	13 (43)	
Hospital	0 (0)	2 (7)	
Nonprofit	0 (0)	1 (3)	
Experience in clinical trials as an investigator			0.15
11 or more trials	11 (73)	13 (43)	
6 to 10 trials	4 (27)	10 (33)	
1 to 5 trials	0 (0)	6 (20)	
0 trials	0 (0)	1 (3)	
Ever authored a systematic review			0.15
Yes	6 (40)	6 (20)	
No	9 (60)	24 (80)	
Ever served on a guidelines panel			0.36
Yes	6 (40)	13 (43)	
No	8 (53)	17 (57)	
Not sure	1 (7)	0 (0)	

^{*} *P* value from a Pearson chi-squared test.

[†] Survey participants may choose to skip questions regarding respondent characteristic.

[‡] Denominator for following questions regarding respondent characteristics.

Table 2

High-Priority Clinical Research Questions and Comparison to 2012 PPP Recommendation's Rating of "Importance to the Care Process"

	Question Number	Clinical Question, Sorted by Median	2012 PPP Rating of Importance to the Care Process
Questions Where 75% of Respondents Assigned a Rating >5			
Questions Prioritized as "Important"	Question 52	Is anti-VEGF therapy effective, for patients with high-risk PDR?	Not Applicable *
	Question 72	Are intravitreal therapies, including corticosteroids and anti-VEGF agents, effective when laser photocoagulation cannot be safely administered, for patients with high-risk PDR?	No Rating †
	Question 51	Is anti-VEGF therapy effective, for patients with non-high-risk PDR?	Not Applicable *
	Question 58	Is anti-VEGF therapy more effective than repeat PRP or repeat vitrectomy, for high-risk PDR?	Not Applicable *
	Question 57	Is anti-VEGF therapy more effective than repeat PRP or repeat vitrectomy, for patients with non-high-risk PDR?	Not Applicable *
	Question 71	Are intravitreal therapies, including corticosteroids and anti-VEGF agents, effective when laser photocoagulation cannot be safely administered, for patients with non-high-risk PDR?	No Rating †
	Question 99	Are there useful biomarkers that are predictive of functional outcomes in the diabetic eye?	Not Applicable ‡
	Question 38	Is pars plana vitrectomy effective in patients with diffuse macular edema unresponsive to focal/grid laser treatment and substantial vitreoretinal traction?	No Rating †
	Question 82	Is anti-VEGF therapy more effective than vitrectomy in patients with untreated PDR and vitreous opacification?	Not Applicable *
Questions Where 75% of Respondents Assigned a Rating of 5			
Question Prioritized as "Moderately Important"	Question 15	Is fluorescein angiography conducted prior to laser surgery effective at identifying treatable lesions of the foveal avascular zone, which may be useful in planning treatment for patients with macular edema involving the center of the macula?	Level A §
	Question 16	Is fluorescein angiography conducted prior to laser surgery effective at identifying pathologic enlargement of the foveal avascular zone, which may be useful in planning treatment for patients with macular edema involving the center of the macula?	Level A §
	Question 93	Are there useful biomarkers that are predictive of anatomic outcomes in the diabetic eye?	Not Applicable ‡
	Question 94	Is telemedicine more cost effective than annual exam for mild NPDR?	Not Applicable ‡
	Question 73	Is early laser photocoagulation more effective than early anti-VEGF therapy for severe NPDR and non-high-risk PDR?	Not Applicable *
	Question 44	Is vitrectomy, with anti-VEGF agents, effective for preserving visual acuity and quality of life in patients with high-risk PDR and NVI/NVA?	No Rating †
	Question 100	Is telemedicine screening with color fundus photos on a nonmydriatic camera noninferior to an office exam for detecting the presence of diabetic retinopathy?	Not Applicable ‡

Question Number	Clinical Question, Sorted by Median	2012 PPP Rating of Importance to the Care Process
Question 104	Is combined optical coherence tomography imaging and fundus photography screening more effective than the current standard of care for detecting diabetic vision-threatening disease?	Not Applicable [‡]
Question 17	Is re-examination at 2–4 month intervals more effective than examination at longer intervals for patients with severe NPDR?	Level A [§]
Question 18	Is re-examination at 2–4 month intervals more effective than examination at longer intervals for patients with non-high-risk PDR?	Level A [§]
Question 36	Is fluorescein angiography-guided panretinal photocoagulation more effective than panretinal photocoagulation without fluorescein angiography for patients with high-risk PDR and macular edema involving the center of the macula?	No Rating [†]
Question 12	Does re-examination every 3–4 months lead to earlier detection and treatment of macular edema compared with examinations at longer intervals of when eyes are symptomatic for patients with diabetes without macular edema involving the center of the macula?	Level A [§]
Question 10	Is re-examination at 6- to 12- month intervals effective compared with examinations at longer intervals or when eyes are symptomatic for patients with retinal microaneurysms and occasional blot hemorrhages or hard exudates, for patients with mild to moderate NPDR without macular edema?	Level A [§]

anti-VEGF = anti-vascular endothelial growth factor; NVI/NVA = neovascularization of the iris/neovascularization of the angle; NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; PPP = preferred practice patterns.

* Question modified through consultation with ophthalmologist (NB).

[†] Question derived from recommendations with no rating provided in the 2012 PPP.

[‡] Question suggested by survey respondents in Round 1 (“write-in” questions).

[§] Question derived from recommendations with rating provided in the 2012 PPP (A = Most Important).